



Infectious meningitis and encephalitis in adults in Denmark

a prospective nationwide observational cohort study (DASGIB)

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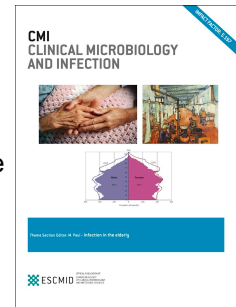
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Abstract

Objectives: To monitor epidemiological trends of infectious meningitis (bacterial and viral) and encephalitis in Denmark.

Methods: Nation-wide prospective observational study of all cases with proven community-acquired infectious meningitis and encephalitis in adults treated in all departments of infectious diseases in Denmark from 1st of January 2015 to 30th of June 2016. We included data on symptoms, aetiology, treatment and outcome assessed by the Glasgow Outcome Scale (GOS) 30-days after discharge. GOS 1-4 was categorised as unfavourable outcome.

Results: During 18 months of observation, we identified 252 cases of viral meningitis (3.6/100,000/year), 214 cases of bacterial meningitis (3.1/100,000/year), and 96 cases of infectious encephalitis (1.4/100,000/year). In bacterial meningitis, *Streptococcus pneumoniae* was most frequent (n=101) followed by *Staphylococcus aureus* (n=24) and β -haemolytic streptococci (n=14). Meningococcal meningitis was rare (n=11). In encephalitis, Herpes simplex virus-1 was most common (n=37) followed by Varicella zoster virus (n=20), while Varicella zoster virus (n=61) was most common in viral meningitis followed by enterovirus (n=50) and Herpes simplex virus-2 (n=46). Case fatality and unfavourable outcome occurred in 31/214 (15%) and 96/214 (45%) with bacterial meningitis and in 5/96 (5%) and 55/89 (62%) with encephalitis. For viral meningitis, unfavourable outcome occurred in 41/252 (17%).

Conclusions: The epidemiology and clinical presentation of the examined central nervous system (CNS) infections differed considerably and bacterial meningitis was more frequent than previously estimated. Overall prognosis remains poor for bacterial meningitis and encephalitis. Prospective nationwide clinical databases of CNS infections may be superior to epidemiological monitoring based on notifications or laboratory systems.

Introduction:

Central nervous system (CNS) infections range from mild-moderate viral meningitis to life-threatening diseases like acute bacterial meningitis or Herpes simplex virus encephalitis. Due to the relative rarity of the diseases, most contemporary studies rely on retrospective retrieval of information with inherent limitations. The majority of studies have examined selected CNS infections and some were hampered by incomplete inclusion and notification systems [1-9]. Although viral meningitis is generally considered a benign disease, some studies suggest that subsequent cognitive impairment may be more prevalent than first assumed [10,11]. Bacterial meningitis and encephalitis remain severe diseases with case-fatality rates of 10-30% and unfavourable outcomes in 40-60% [1,3,4,12].

Therefore, an overview of the burden of CNS infections is important and given the rarity of CNS infections, well-established multi-centre networks are required to carry out future clinical studies. In order to address these questions and to monitor epidemiological trends, we aimed to establish a high-quality prospective observational database of all CNS infections treated at departments of infectious diseases in Denmark. In the current study, we set out to examine the epidemiology, clinical characteristics and outcome of infectious meningitis and encephalitis.

Methods:

Setting

The Danish Study Group of Infections of the Brain (DASGIB) was established in January 2014 as a nationwide collaboration between infectious disease specialists with the aim to monitor epidemiological trends and conduct studies of CNS infections in Denmark. The parties agreed to prospectively register all CNS infections diagnosed and/or treated at all seven departments of infectious diseases in Denmark using a web-based case-report form (CRF). To ensure completeness of reported CNS infections annual searches of selected ICD-10 codes (Supplementary Table 1) are performed in local administrative databases at each department. According to the Danish Board of Health, all patients with CNS infections are to be treated at departments of infectious diseases. In general, diagnostic work-up and treatment were left at the discretion of the local physician and therefore not standardised. For bacterial meningitis, national guidelines are available (www.infmed.dk/udgivelser - in Danish). Serum procalcitonin levels are not routinely used for CNS infections in Denmark.

In Denmark, all inhabitants are assigned a unique personal identifier at birth or immigration by which all health-care information can be obtained at an individual-based level. Treatment in primary, secondary and tertiary care is tax-financed and free of charge at the point of delivery. The population above 15 years of age in Denmark was 4,628,949 in January 2015 and 5,659,715 for the entire population [13].

Study population

All patients above 15 years of age were prospectively included in the DASGIB cohort by the principal investigator at each site if they had a clinical presentation suggestive of CNS infection (e.g. any combination of neck stiffness, fever, headache or altered mental status) and either (i) Positive CSF culture or positive bacterial/viral DNA-based analysis for (community-acquired) pathogens in the CSF or (ii) a positive blood culture and CSF leukocytes $>10/\text{mL}$ or (iii) CSF leukocytes $>10/\text{mL}$ without any alternative diagnoses more likely to explain the patients' conditions. Exact definitions of the included CNS infections as well as vaccinations policies for CNS pathogens are provided in the supplementary material. Quality control of case enrolment was ensured by ad hoc case-to-case discussions and at study group meetings 2-3 times a year. During data management for this study, local investigators were queried if case report forms contained outliers or unusual values. We excluded patients with hospital-acquired CNS infections as defined by the Centers for Disease Control and Prevention [13] or an implanted neurosurgical device. This study examined patients included during 18 months from 1st of January 2015 until 30th of June 2016.

Patient data

We prospectively recorded baseline information on demographics, time and place of admission, exposures, as well as clinical signs and symptoms at day of admission. Confusion was defined as disorientation in person, time or place at admission. Patients were categorised with an altered mental status at admission if the Glasgow Coma Scale (GCS) was below 14. During the course of hospitalization we noted antimicrobial treatment, cranial imaging and laboratory results from the departments of biochemistry, radiology and microbiology. Time of admission was obtained in prioritised order from the ambulance charts or notifications of arrival by secretaries or nurses in the emergency departments. Timing of lumbar puncture and cranial imaging was extracted from the electronic records at the departments of

biochemistry or radiology while timing of antibiotic therapy for meningitis was identified in electronic medication systems. Time to lumbar puncture, cranial imaging and antibiotic therapy was calculated as time from arrival at hospital to each of the above events.

At 30 days after discharge outcome was assessed according to the Glasgow Outcome Scale (GOS): 1. Death, 2. A vegetative state, 3. Severe sequelae and dependency upon others in daily life, 4. Moderate sequelae but with the ability to live independently, and 5. No or only mild sequelae [14]. GOS scores of 1-4 were considered unfavourable outcome.

Statistical analyses

Contingency tables were constructed to describe baseline demographics. Proportions are presented as n/N with 95% confidence intervals (95% CIs) and continuous variables as medians with interquartile ranges (IQR). We used Stata MP® version 14.2 for statistical analyses.

Ethical considerations

The Danish Data Protection Agency approved the DASGIB cohort (record no. 2012-58-0018) and establishment of a biobank of CSF and blood samples from these patients (record no. 2013-41-2502). Approval from the Danish Board of Health or an ethical committee was not required for this study. The study is reported according to STROBE guidelines.

Results:

During 1.5 years of study, we observed 252 cases of viral meningitis (3.6/100,000/year), 214 cases of bacterial meningitis (3.1/100,000/year) and 96 cases of encephalitis (1.4/100,000/year). A few survivors at discharge were tourists (n=2) and thus unavailable for 30-day follow-up.

Patients with bacterial meningitis presented with neck stiffness in 111/197 (56%), altered mental status in 152/201 (76%) and fever $\geq 38.0^{\circ}\text{C}$ in 140/204 (69%) of patients (Table 1). The meningitis triad (neck stiffness, altered mental status and fever) was present in 59/214 (28%) of patients. We observed a median CSF leukocytes of $937 \times 10^6/\text{mL}$ (IQR 231-4137), a median CSF protein of 2.3 g/L (IQR 1.0-5.1) and a median CSF:blood glucose index of 0.26 (IQR 0.04-0.48). The aetiology was predominated by *Streptococcus pneumoniae*

(1.5/100,000/year), *Staphylococcus aureus* (0.3/100,000/year) and β -haemolytic streptococci (0.2/100,000/year) (Table 2). Twelve patients presented with symptoms of CNS infection at admission and had concomitant endocarditis of which eight were caused by *S. aureus*, two by β -haemolytic streptococci, and one by α -haemolytic streptococcus and *Haemophilus influenzae* each. Another eight patients with bacterial meningitis had concomitant spondylodiscitis of which three were caused by *S. aureus*, two by β -haemolytic streptococci, two by *S. pneumoniae* and one by *Escherichia coli*. In total, 11/24 of cases of *S. aureus* meningitis were associated with either endocarditis or spondylodiscitis.

The median time from admission to lumbar puncture and antibiotic therapy for meningitis was 3.7 hours (IQR 1.8-8.8) and 3.3 (IQR 1.5-10.0), respectively. Cranial imaging was performed before lumbar puncture in 99/214 (46%) of patients and 160/212 (75%) were given empiric adjunctive dexamethasone treatment. In comparison of cases treated with vs. without dexamethasone, case-fatalities were 21/160 (13%) vs. 9/52 (17%), $p=0.45$ and unfavourable outcomes 30-days after discharge were 70/160 (44%) vs. 24/52 (48%), $p=0.7$. Specifically for pneumococcal meningitis treated with or without dexamethasone, case fatalities were 8/85 (9%) vs. 3/15 (20%), $p=0.23$ and unfavourable outcomes 30-days after discharge were 34/85 (40%) vs. 9/15 (60%), $p=0.15$.

Patients with encephalitis presented with headache in 56/76 (74%), fever $\geq 38.0^{\circ}\text{C}$ in 44/91 (48%), altered mental status in 27/71 (38%), seizures in 13/87 (15%) and focal neurological deficits in 13/90 (14%) patients (Table 3). Herpes simplex virus 1 (HSV-1) was the most common pathogen (0.5/100,000/year) followed by Varicella zoster virus (VZV) (0.3/100,000/year) (Table 2). The median time from admission to lumbar puncture, cranial CT and MRI were 13.1 hours (4.2-43.0), 4.2 hours (1.8-24.9) and 64.3 hours (31.5-112.6), respectively. Empiric acyclovir was administered in 90/93 (97%) patients before a formal diagnosis of encephalitis was established. At 30-days after discharge patients with encephalitis had a case fatality of 5/89 (5%) and the proportion with unfavourable outcome was 55/89 (62%).

Patients with viral meningitis had a median age of 36 years (IQR 26-52) and presented with headache in 214/237 (90%), neck stiffness in 107/241 (44%), and fever $\geq 38.0^{\circ}\text{C}$ in 92/236 (39%) of patients (Table 4). The most common aetiology was VZV (0.9/100,000/year)

followed by enterovirus and Herpes simplex virus 2 (0.7/100,000/year for both) (Table 2). Unfavourable outcome 30-days after discharge occurred in 41/245 (17%) patients, of whom 37 (15%) had a GOS of 4 and three had a GOS of 3 (advanced AIDS in two patients). One patient with viral meningitis of unknown aetiology died of a cerebral haemorrhage during hospitalization

Discussion:

We conducted a nationwide prospective observational cohort study of infectious meningitis and encephalitis in all adults diagnosed or treated at the seven departments of infectious diseases in Denmark. Except for a higher incidence of bacterial meningitis and a relatively large proportion caused by *S. aureus* and β -haemolytic streptococcal, the clinical presentations and outcomes were comparable to previous cohorts of each disease from similar settings. Among patients with viral meningitis, 37/252 (15%) had a GOS of 4 at 30-days after discharge suggesting that return to previous lifestyle may take longer than often assumed.

Laboratory-proven or clinically suspected cases of bacterial meningitis and invasive meningococcal disease (i.e. meningitis or sepsis) are notifiable by law in Denmark. Annual reports of incident cases based upon such notifications by clinicians are published by the Statens Serum Institute. We found a higher incidence of bacterial meningitis of 3.1/100,000/year in adults (2.5/100,000/year using the entire population as denominator) than estimates of 2.4/100,000/year in both children and adults (entire population as denominator) from Statens Serum Institut [15]. Such surveillance estimates have previously been shown to be inaccurate with an overall notification rate of 66% in Denmark [16]. Unusual pathogens such as *S. aureus*, *E. coli* and streptococci other than pneumococcus were particularly underreported, whereas the notifications of meningococcal and pneumococcal meningitis were almost complete. The observed difference in reported incidences of bacterial meningitis in our study may also be due to more vigilant inclusion of cases with unusual pathogens and cases with positive blood culture and CSF pleocytosis. Of note, use of DNA-based technologies for diagnosis of bacterial meningitis has not changed during the study period in Denmark.

Among cases of bacterial meningitis, we found that *S. aureus* and β -haemolytic streptococci were the second and third most frequent aetiologies. Although patients presented primarily with signs of CNS infection, a total of 20 cases had either concomitant endocarditis or spondylodiscitis. This is in contrast to a recent prospective study of CSF-culture positive cases in adults from the Netherlands in years 2006-14, where the overall incidence of bacterial meningitis was 0.94/100,000/year and *N. meningitidis* and *L. monocytogenes* were the second and third most frequent pathogens [1]. Two other registry-based studies of bacterial meningitis from the USA (children and adults) and Sweden (adults) also showed that meningococcal meningitis was the second most common cause in their settings [17,18]. The observed rarity of meningococcal meningitis in our cohort is supported by an overall low incidence of invasive meningococcal disease in Denmark notified to Statens Serum Institute [19]. Meningococcal disease is most frequent among children and adolescents and incidences may differ according to e.g. secular variations in study periods, demographic compositions of cohorts and vaccination programmes. Since the median age of the Dutch and Swedish groups was 61 years vs. 65 years in our cohort of adults and meningococcal vaccinations are not part of the childhood vaccination programme in Denmark, we consider secular variations as the most probable reason for the low incidence in our cohort.

Compared to the Dutch cohort our bacterial meningitis patients less often had neck stiffness (56% vs. 74%), a higher GCS score (13 vs. 11), lower levels of CSF-leukocytes ($937 \times 10^6/\text{mL}$ vs. $2310 \times 10^6/\text{mL}$) and CSF-protein (2.3 g/L vs. 3.9 g/L) and higher levels of CSF:blood glucose ratio (0.26 vs. 0.04). This may reflect differences in bacterial aetiologies and inclusion criteria as only CSF-culture positive cases are included in the Dutch cohort, which could possibly be associated with more pronounced CNS inflammation. However, additional studies are needed to examine this finding further. In pneumococcal meningitis, adjunctive dexamethasone was associated with both lower case fatality and fewer unfavourable outcomes although statistical significance was not reached. This is most likely due to sample size limitations and dexamethasone should remain standard therapy for bacterial meningitis [20]

Similar to other studies of encephalitis, we found that HSV-1 (39%) and VZV (21%) were the most frequent pathogens [3,4,21]. Interestingly, mortality at 30-days after discharge was only 5% in our study which is comparable to a registry-based study from the USA in years 2000-

10, but lower than the mortalities from prospective observational cohorts from the UK in years 2005-6 (12%) and France in year 2007 (10%).

There are several limitations in our study. Selection bias may be present as patients had to have a lumbar puncture at some point during admission to be included and some cases e.g. viral meningitis may be diagnosed and treated at other departments than infectious diseases. This suggests that incidences could be higher than our estimates. However, according to the Danish Board of Health, the departments of infectious diseases are responsible for care of all patients with CNS infections, even when admitted to the intensive care unit, whereby such inaccuracies in incidences should be limited. Some patients were transferred from other hospitals to the department of infectious diseases and availability of all clinical information at admission may have been restricted in spite of the prospective design of our cohort. Although all patients with CNS infections are scheduled to at least a 30-day follow-up after discharge not all patients showed up for these visits. Still, given the unique civil registration number and setup of the Danish health care system, information on mortality and re-admissions are available, which strengthens estimates of mortality and curtails any missed serious new sequelae after discharge. Lastly, patient management including diagnostic measures and treatment was not standardised which may result in local differences in proportions with proven aetiologies and outcome of disease.

In conclusion, the epidemiology and clinical presentation differed considerably among the examined CNS infections. Bacterial meningitis was more frequent than in previous studies with a considerable proportion caused by *S. aureus* and beta-haemolytic streptococci of which many had concomitant distant foci. Secular variation is a likely cause of few cases of meningococcal disease. Outcome remains poor for bacterial meningitis and encephalitis. Prospective nationwide clinical databases of CNS infections may be superior to epidemiological monitoring based on notifications or laboratory systems.

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Conflicts of interests: None.

Author contribution: JB and HN conceived the study and analysed the data. JB wrote the first draft. JB, HN, MS, LL, LW, JHL, AL, CB collected data and participated in a critical review of the manuscript. CØ also participated in conceptualisation of the study and critical review of manuscript.

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Table 1:

Clinical characteristics at admission and outcome of 214 patients with bacterial meningitis. Categorical variables are presented as n (%) and continuous variables as medians with interquartile rates (IQRs).

Characteristic	Observed patients (N)	n (%), median (IQR)
Age (years)	214	65 (54-73)
Sex (females)	214	102 (48)
Comorbidity*	210	67 (32)
Duration of symptoms (days)	214	1 (0.4-3)
Headache	158	123 (78)
Neck stiffness	197	111 (56)
Nausea/vomiting	187	62 (33)
Seizures	190	19 (10)
Petechiae/rash	197	23 (12)
Fever ($\geq 38.0^{\circ}\text{C}$)	204	140 (69)
GCS	167	13 (10-15)
Confusion	201	152 (76)
Altered mental status (GCS<14)	167	97 (58)
Focal neurological deficit	208	24 (12)
Systolic blood pressure (mm Hg)	200	143 (121-165)
CRP (mg/L)	209	188 (80-284)
B-leukocytes ($10^9/\text{mL}$)	209	13.9 (9.8-19.3)
B-thrombocytes ($10^9/\text{mL}$)	200	205 (142-263)
CSF		
Leukocytes ($10^6/\text{mL}$)	210	937 (231-4137)
- Polymorphonuclear ($10^6/\text{mL}$)	196	709 (158-3685)
Protein (g/L)	199	2.3 (1.0-5.1)
Glucose index	179	0.26 (0.04-0.48)
Lactate (mmol/L)	63	11.2 (5.1-15.0)
Cranial imaging during admission	214	154 (72)
Infarction	154	33 (21)

Opacification of ear, sinus or mastoid	154	23 (15)
Otitis media/mastoiditis	154	15 (10)
Sinusitis	154	11 (7)
Intracranial haemorrhage	154	6 (4)
Generalised oedema	154	6 (4)
Hydrocephalus	154	5 (3)
Other findings**	154	11 (7)
Cranial imaging before lumbar puncture	214	99 (46)
Time to lumbar puncture (hours)	201	3.7 (1.8-8.8)
Time to antibiotics (hours)	200	3.3 (1.5-10.0)
Adjunctive dexamethasone	212	160 (75)
Intensive care unit admission (ICU)	214	96 (45)
Outcome		
Case fatality rate	214	31 (15)
In patients admitted to ICU	96	20 (21)
Unfavourable outcome 30-days after discharge	214	96 (45)

GCS: Glasgow coma scale, CRP: C-reactive protein, CSF: Cerebrospinal fluid.

*Comorbidity: Alcohol abuse, diabetes mellitus, solid or haematological cancer (including malignant melanoma, excluding other skin cancers), congenital or acquired immunodeficiency including HIV. **Includes six cases with ventriculitis, four with benign tumours, three with secondary brain abscess, three with secondary subdural empyema, two with hygroma, one with cerebritis, and one with malignant tumour and dural leakage each.

Table 2: Causative pathogens of infectious meningitis and encephalitis in adults treated in departments of infectious diseases in Denmark. Data is presented as n (%).

Central nervous system infection	Observed patients (N)	Causative pathogen
Bacterial meningitis		
Proven aetiology	214	183 (86)
<i>S. pneumoniae</i>	-	101 (47)
<i>S. aureus</i>	-	24 (11)
β -haemolytic streptococci	-	14 (7)
<i>N. meningitidis</i>	-	11 (5)
α -haemolytic streptococci	-	8 (4)
<i>E. coli</i>	-	8 (4)
<i>L. monocytogenes</i>	-	7 (3)
Other*	-	10 (5)
Encephalitis		
Proven aetiology	96	64 (67)
HSV-1	-	37 (39)
VZV	-	20 (21)
HSV-2	-	3 (3)
HIV	-	2 (2)
TBE	-	1 (1)
EBV	-	1 (1)
Viral meningitis		
Proven aetiology	252	163 (65)
VZV	-	61 (24)
Enterovirus	-	50 (20)
HSV 2	-	46 (18)
EBV	-	2 (1)
Chikungunya (traveller)	-	1 (1)
HIV	-	1 (1)
Influenza	-	1 (1)

TBE

-

1 (1)

HSV 1= Herpes simplex virus 1, VZV=Varicella zoster virus, HSV 2=Herpes simplex virus 2, HIV=Human immuno-deficiency virus, TBE=Tick-borne encephalitis virus, EBV=Epstein-barr virus.

Table 3:

Clinical characteristics at admission and outcome of 96 patients with infectious encephalitis. Categorical variables are presented as n (%) and continuous variables as medians with interquartile rates (IQRs).

Characteristic	Observed patients (N)	n (%), median (IQR)
Age (years)	96	65 (43-76)
Sex (males)	96	42 (44)
Comorbidity*	93	20 (22)
Duration of symptoms (days)	96	3 (1-5.5)
Headache	76	56 (74)
Nausea/vomiting	87	30 (34)
Fever ($\geq 38.0^{\circ}\text{C}$)	91	44 (48)
Confusion	94	69 (73)
Altered mental status (GCS<14)	71	27 (38)
Focal neurological deficit	90	13 (14)
Seizures	87	13 (15)
GCS	71	14 (12-15)
Systolic blood pressure (mm Hg)	91	140 (126-156)
CRP (mg/L)	92	5 (2-13)
B-leukocytes ($10^9/\text{mL}$)	95	9.5 (7.7-11.5)
CSF		
Leukocytes ($10^6/\text{mL}$)	96	87 (39-178)
- Polymorphonuclear ($10^6/\text{mL}$)	81	2 (0-8)
Protein (g/L)	93	0.7 (0.5-1.1)
Glucose index	66	0.57 (0.47-0.64)
Lactate (mmol/L)	29	2.7 (2.1-3.0)
MRI suggestive of encephalitis	80	46 (58)
Time to lumbar puncture (hours)	90	13.1 (4.2-43.0)
Time to cranial CT (hours)	72	4.2 (1.8-24.9)
Time to cranial MRI (hours)	74	64.3 (31.5-112.6)
Cranial imaging before lumbar	96	59 (61)

puncture		
Empiric acyclovir treatment**	93	90 (97)
Empiric adjunctive dexamethasone**	79	25 (32)
Intensive care unit admission	95	24 (25)
Outcome		
Case fatality rate	96	5 (5)
In patients admitted to ICU	24	1 (4)
Unfavourable outcome 30-days	89	55 (62)
after discharge		

GCS: Glasgow coma scale, CRP: C-reactive protein, CSF: Cerebrospinal fluid.

*Comorbidity: Alcohol abuse, diabetes mellitus, solid or haematological cancer (including malignant melanoma, excluding other skin cancers), congenital or acquired immunodeficiency including HIV. **Initiated before the aetiology was established.

Table 4:

Clinical characteristics at admission and outcome of 252 patients with viral meningitis. Categorical variables are presented as n (%) and continuous variables as medians with interquartile rates (IQRs).

Characteristic	Observed patients (N)	n (%), median (IQR)
Age (years)	252	36 (26-52)
Sex (males)	252	119 (47)
Comorbidity*	244	28 (11)
Duration of symptoms (days)	252	2 (1-5)
Headache	237	214 (90)
Neck stiffness	241	107 (44)
Nausea/vomiting	242	92 (38)
Seizures	238	5 (2)
Fever ($\geq 38.0^{\circ}\text{C}$)	236	92 (39)
Confusion	243	43 (17)
GCS	212	15 (15-15)
Systolic blood pressure (mm Hg)	229	130 (120-141)
CRP (mg/L)	242	4 (2-15)
B-leukocytes ($10^9/\text{mL}$)	244	8.5 (6.7-10.7)
CSF		
Leukocytes ($10^6/\text{mL}$)	252	125 (37-270)
- Polymorphonuclear ($10^6/\text{mL}$)	225	6 (1-30)
Protein (g/L)	246	0.7 (0.5-1.0)
Glucose index	192	0.55 (0.49-0.62)
Lactate (mmol/L)**	88	2.2 (1.8-2.8)
Cranial imaging before lumbar puncture	252	84 (33)
Empiric acyclovir treatment	240	203 (85)
Empiric adjunctive dexamethasone	206	86 (42)
Time to lumbar puncture (hours)	237	3.8 (1.5-8.4)

Outcome

Case fatality rate	252	1
Unfavourable outcome 30-days after discharge	245	41 (17)

GCS: Glasgow coma scale, CRP: C-reactive protein, CSF: Cerebrospinal fluid.

*Comorbidity: Alcohol abuse, diabetes mellitus, solid or haematological cancer (including malignant melanoma, excluding other skin cancers), congenital or acquired immunodeficiency including HIV. **Only a few centres perform CSF-lactate analyses.

Supplementary material:

The Danish Study Group of Infections of the Brain (DASGIB) consists of:

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Henrik Nielsen, Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark (Chair)

Supplementary Table 1:

Codes used for assessment of completeness of reported CNS infections. International Classification of Diseases (ICD), 10th version.

A17
A32.1
A32.7
A39.0
A52.1-52.3
A69.2
A83
A84
A85
A87
A89
B00.3-00.4
B01.0-01.1
B02.0-02.9
B582
B451
B375
G00
G01
G02
G03
G04
G05
G06
G07

Definitions of central nervous system infections used in the Danish Study Group of Infections of the Brain.

For all cases with unproven pathogens, no alternative diagnosis than CNS infection was thought more likely after completed multidisciplinary diagnostic work-up.

Viral meningitis: A clinical presentation with non-bacterial meningitis (e.g. headache, neck stiffness, photo- or phonophobia, fever) and cerebrospinal fluid leukocytes > 10 cells/mL. We included both proven and suspected viral infections. For patients with undetermined pathogen CSF leukocytes > 10/mL was mandatory and the principal investigator used all available information to conclude whether the infection was most likely bacterial or viral. In case of doubt, patients were discussed with the DASGIB secretary and chair or at meetings.

Bacterial meningitis: A clinical presentation consistent with bacterial meningitis (e.g. headache, neck stiffness, fever, altered mental status) and proven bacterial aetiology (CSF or blood culture/DNA based technology or antigen tests). For patients in whom the bacteria could not be cultured or identified by DNA-based technologies, CSF leukocytes > 10/mL was mandatory and the principal investigator used all available information to conclude whether the infection was most likely bacterial or viral. In case of doubt, patients were discussed with the DASGIB secretary and chair or at meetings. Patients with mycobacterial meningitis were omitted for this study.

Infectious encephalitis: A clinical presentation consistent with encephalitis (e.g. headache, fever, focal neurological deficit, altered mental status >24 hours) as defined the International Encephalitis Consortium (Venkatesan A, Tunkel AR, Bloch KC, Laming AS, Sejvar J, Bitnun A, et al. Case Definitions, Diagnostic Algorithms, and Priorities in Encephalitis: Consensus Statement of the International Encephalitis Consortium. Clin Infect Dis 2013;57:1114–28. doi:10.1093/cid/cit458.). We excluded cases of proven or suspected autoimmune encephalitis.

Danish vaccination programmes for pathogens known to cause CNS infections:

- Childhood vaccination programme
 - o Diphtheria-tetanus-pertussis-polio-*H. influenzae* and 13-valent conjugated pneumococcal vaccines at 3, 5 and 12 months of age. A booster of diphtheria-tetanus-pertussis-polio is given at 5 years of age.
 - o Measles, mumps and rubella are administered at 15 months of age with a booster at 4 years of age.
 - o Conjugated vaccination for *H. influenzae* was introduced in 1993. For *S. pneumoniae*, a 7-valent conjugated vaccine was introduced in 2007 and replaced by a 13-valent vaccine in 2010. For pneumococcal vaccinations in adults please see below.
- Recommendations of vaccination of risk groups in Denmark (adults and children):

- Conjugated meningococcal vaccines (Quadrivalent A, C, Y, W-135 and lately also specific conjugated vaccine for serogroup B) have been given to house-hold relatives of confirmed invasive meningococcal disease, but has never been part of the Danish childhood vaccination programme.
 - Since 2014, 13-valent conjugated pneumococcal vaccine is strongly recommended to patients with asplenia, cochlear implants, before organ transplantation, dural defects, immunosuppressive conditions (e.g. HIV or lymphoma) or after documented invasive pneumococcal disease (e.g. pneumonia, meningitis, bacteraemia). Eight weeks later a second vaccination with the 23-valent polysaccharide pneumococcal vaccine is advised.
- In Denmark, pneumococcal vaccination can also considered in patients with chronic heart failure, chronic obstructive pulmonary disease, chronic liver- or kidney disease, diabetes mellitus, age > 64 years, asthma, b-cell immuno-deficiency, smokers, occupational hazards (e.g. welders).